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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/724,889	11/28/2000	Bryan Julien	300622003111	7394

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EXAMINER	
NASHED, NASHAAT T	

ART UNIT	PAPER NUMBER
1652	16

DATE MAILED: 05/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/724,889	Julien et al.
Examiner	**Art Unit**
Nashaat T. Nashed	1652

-- *The MAILING DATE of this communication appears on the cover sheet with the correspondence address* --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Apr 21, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *15-17, 25, and 29-34* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *15-17, 25, and 29-34* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *10 & 13*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

The application has been amended as requested in the communication filed April 21, 2003. Accordingly, claims 1-4, 18-24, and 26-28 have been canceled; claims 15-17, and 25 have been amended; and claims 29-34 have been entered.

Applicant's election with traverse of Group VI, claims 15-17, and 25, drawn to modified epoE, in Paper No. 15 is acknowledged. The traversal is on the ground(s) that claims are drawn to a complete modified functional epothiolone polyketide synthase (PKS) that is able to make polyketide and that the examination of a modification at several portion of the complete polyketide synthase is sufficiently limited and does not impose a search burden. Applicants arguments have been fully considered, but they are found unpersuasive. The epothiolone polyketide synthases the product of *epoA-epoE* genes are independent chemical entities having different structure and function and each of which contains several independent enzymatic activities. Thus, examining Groups I-VI represent a search burden on the examiner because each of the open reading frame has to be searched in the patent and non-patent literature. As a matter of fact, each modification to each polyketide synthase epoA-epoE would require separate search. Applicants should keep in mind the epoA-epoE are huge proteins, e. g., epoE is 7257 amino acid, each of which comprises large number of enzymatic activity wherein each enzymatic activity is comprised in a domain that can functional independently or in a chimeric polyketide synthase, see claims 24 and 25.

The requirement is still deemed proper and is therefore made **FINAL**.

Claims 15-17, 25, and 29-34 are under consideration.

This application appears to have been filed with informal drawings which are acceptable for examination purposes only. The drawing of low quality. Formal drawings is required.

The specification has not been checked to the extent necessary to determine the presence of all possible minor errors. Applicant's cooperation is requested in correcting any errors of which applicant may become aware in the specification.

Claim 30 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. The native acyl transferase (AT) domain of modules 7 and 8 has specificity for methymalonyl. Said AT domains are known to accept other malonyl derivatives such as malonyl, ethyl malonyl and 2-hydroxymalonyl as substrates. Neither the prior art or the specification teach AT domains which are specific to malonyl, ethylmalonyl or 2-hydroxymalonyl. Thus, claim 30 does not further limit claim 29.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 15-17, 25, 30, 31, and 34 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The following are the reasons for the rejections:

(a) claims 15 and 25 contain the undefined abbreviations and acronyms AT, KR, DH, ER, and MT. Abbreviations and acronyms must be defined at least once in the claims. For examination purposes only, it is assumed that the meaning of the abbreviation are: (a) AT: acyltransferase, (c) KR: ketoreductase, (d) ER: enoylreductase, and (e) MT: methyl transferase.

(b) The phrase "inactivation of at least one activity in at least one β-carbonyl modification domain in module 7" in claim 15 renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase is indefinite because module 7 contains only one β-carbonyl modification domain, i. e., ketoreductase 7.

(c) The clause "specificity of the acetyl transferase (AT) domain in module 7 is malonyl ....*etc*" renders the claim indefinite and confusing because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. The phrase "acetyl transferase" in claim 30 is indefinite because there are five different epothiolone synthases. The claim is confusing because the specificity of an acetyl transferase is the acyl group of acetic acid by definition and the nomenclature of the enzymatic activity. For examination purposes only, the phrase is taken to mean "acyl transferase".

(d) Claim 30 recites the limitation "wherein the specificity of the ac[et]yl transferase domain in module 7" in line 2. There is insufficient antecedent basis for this limitation in the claim. The claim is dependent on claim 29 wherein the phrase AT domain does not appear any where. For examination purposes only, it is assumed that the claim is dependent from claim 15.

(e) Claim 31 recites the limitation "that lacks the methyl transferase (MT) activity of module 8". There is insufficient antecedent basis for this limitation in the claim. The claim is dependent on claim 29 wherein the phrase MT activity does not appear any where. For examination purposes only, it is assumed that the claim is assumed to be directed to epoE missing the MT domain.

(f) The phrase "derivatives thereof" in claim 34 renders the claim indefinite because the resulting claim does not clearly set forth the metes and bounds of the patent protection desired. For examination purposes only, the phrase is disregarded.

(g) Claims 16 and 17 are included with these rejections because they are dependent on a rejected claim and do not cure its deficiencies.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 15-18, 25, and 29-34 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 15-18 and 29-34 are directed to modified epoE, the product of the *eopE* gene, isolated from any biological source have any structure. Claim 25 is directed to any polyketide synthase comprising the methyl transferase domain of presumably module 8 of epoE. The specification, however, only provides a single representative species of the epoE from *Sorangium cellulosm* encompassed by these claims. There is no disclosure of any particular structure to function/activity relationship in the single disclosed species. The specification also fails to describe additional representative species of these epoE by any identifying structural characteristics or properties other than the enzymatic activities recited in the table on page 52 and the nucleic acid encoding said activities listed in the table on pages 14 and 15, for which no predictability of structure is apparent. Given this lack of additional representative species as encompassed by the claims, Applicants have failed to sufficiently describe the claimed invention, in such full, clear, concise, and exact terms that a skilled artisan would recognize Applicants were in possession of the claimed invention.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 15-17, 25 and 29-34 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schupp *et al.* (Schupp, IDS paper number 13, Ref.No. 5, U. S. Patent 6,355,459) in view Khosla *et al.* (Khosla A, IDS reference, paper number 10, reference number 10, U. S. Patent 6,391,594), and Khosla *et al.* (Khosla B, IDS paper number 11, Ref No. 33: WO 97/02358).

Schupp teach the gene cluster for the biosynthesis of epothilones from *Sorangium cellulosum* (SEQ ID NO: 1), see the abstract. They identified 22 open reading frames in the nucleic acid sequence of SEQ ID NO: 1 which are listed in Table 1, see the Table bridging column 29 and 30. In particular, they identified an open reading frame corresponds to residues 43,524-54,920 which they call epoD encoding the 3,798 amino acid of SEQ ID NO: 6 and containing two modules, see column 33, lines 22 to column 34, line. Specifically, they teach the specificity of the AT domain of both modules is for methylmalonyl as well as the methytransferase domain in the second module. Also, they identified all catalytic and functional activities of the epoD gene products, see column 33, lines 7-61. The epoD gene taught by Schupp appears to be identical or functionally equivalent to the epoE of the instant application. The genes are isolated from the same biological source and encoding for the same enzymatic activities. Schupp teach the recombinant expression of epothilone gene cluster in a host cell such as *Streptomyces coelicolor*, example 13 and the isolation of epothilone from the host cell culture, see example 14. In addition, they teach that epothilone have narrow antifungal spectrum and mimic the activity of taxol as an anticancer agents, see column 2, lines 45-67.

Khosla A teach the modification of polyketide synthases using to produce new derivatives of polyketides. Example 2 teaches the replacement of DEBS modules by rapamycin modules and the replacement of DEBS AT2 domain by rapAT2 domain. Example 3 teach the deletion of β-carbonyl modifying activity. Example 5 teaches manipulation of macrolide ring size by inserting a thioesterase after the last module of the biosynthetic pathway. In each modification, a new polyketide compound is obtained.

Khosla B teach a cell free system for the synthesis of polyketides from modified DEBS, see in particular example 7.

Schupp and Khosla A provide one of ordinary skill in the art with motivation at the time of invention to modify an epothilone polyketide synthase. Schupp teach the antifungal and anticancer activities of epothilone derivatives. Khosla A teach that the modification of a polyketide synthase produces new derivatives of polyketides which can be made by a designed biosynthetic pathway that include deletion or substitution of enzymatic activities including acyl transferase, keto reductase, enoyl reductase, and dehydratase activities. Thus, it would have been obvious to one of ordinary skill in the art at the time of invention to obtain the nucleic acid sequence encoding epoD (epoE of the instant application) as taught by

Schupp, replace the AT domain by another having different specificity, inactivate β-carbonyl modifying activity or add additional β-carbonyl modifying activities by the teaching of Khosla A (claims 15, and 29-31). Once the ordinary skill in the art obtained the nucleic acid encoding the modified epoD/E, he/she would have inserted the nucleic acid sequence into a host cell, expressed the modified epoD/E, isolated the epoD/E and utilized the modified epoD/E in an *in vitro* method such as that taught by Khosla B to make novel epothiolone. The method would have included other polyketide synthases and other modifying enzymes from the epothilone biosynthetic pathway taught by Schupp (claims 16, 17, and 32-34). Similarly, one of ordinary skill in the art would have been further motivated by the teaching of Khosla A to use the two modules and their domains of the to modify other polyketide synthases such as those of DEBS polyketide synthase to obtain new derivatives and analogs of 6-DB. Thus, the ordinary skill in the art would use the teachings of Khosla A to generate new modified DEBS in order to use them in a method to make new molecules (claim 25). Thus, the claimed invention was within the ordinary skill in the art to make and use at the time was made and was as a whole, clearly *prima facie* obvious.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nashaat T. Nashed, Ph. D. whose telephone number is (703) 305-6586. The examiner can normally be reached Monday, Tuesday, Thursday, and Friday from 9:00 a.m. to 5:30 p.m.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can be reached on (703) 308-3804. The fax phone numbers for this Group are (703) 305-3014 and (703)308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Nashaat T. Nashed, Ph. D.
Primary Examiner